BIOENGINEERING: SHORT TERM OPTIMISM AND LONG TERM RISK

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Whatever our background or occupation, most of us do not hesitate to make profound statements on philosophical and ethical matters. The subject of our current conference -- "Manipulating Life; Medical Advances and Human Responsibility" -- is ideal for crystal ball gazing. The technology of gene transfer and modification is very much in a state of flux, and the medical and evolutionary consequences are unpredictable. It would be difficult to rule out any reasonable prognostication.

Quite by accident, I came across a lecture by an old friend, Ernst Chain, who shared the Nobel Prize for the discovery and production of penicillin, in which he gives his opinion on the use of genetic engineering in man. The lecture was given just six years ago, in 1977. I would like to quote from the remarks by this eminently reasonable man:

> There exists no method, at present, nor is there the likelihood that one will be discovered in the foreseeable future, by which it would be possible to alter the nucleotide sequence, and thereby the genetic properties, in any gene of any mammalian cell in a <u>controlled</u> manner which could be termed 'genetic engineering.' Any speculations that such a process may be near at hand and could influence the heredity of man must be dismissed as science fiction.

The unpredictability of discovery in a fast-moving field such as mammalian genetics is underlined by recent observations in exactly the field of research that Professor Chain considers in this quotation. We have all read or heard about the production of "giant mice" by genetic engineering. In these experiments, the gene for mouse growth hormone was injected into mouse eggs that had been fertilized, and the eggs were then allowed to mature in utero. The resulting animals apparently looked more like rats than mice, and the whole experiment is not only interesting but somewhat amusing. This experiment emphasizes how quickly the development of new techniques for the preparation and study of biological materials can lead to astounding biological results. The next step, of course, will be a set of similar experiments on cattle and sheep, and other animals of interest to man. The very existence of the "giant mouse" experiment immediately predicts that similar experiments could be done with humans. The controlled injection of the gene for human growth hormone into fertilized human ova could easily lead, in twenty years, to a Minnesota football team made up entirely of nine-foot players. Although the experiments I have just mentioned have a certain humorous quality, I will, in this lecture, take a moderately gloomy view of the possible undesirable consequences of genetic engineering as applied to man.

Being a scientist, myself, I have some insight into what makes a research worker tick. The qualities that characterize and motivate a good scientist do not necessarily have any bearing on the ethical or sociological sequelae of discovery. An investigator who is worth his salt will attack an interesting problem for its own sake, and with increasing enthusiasm as the project proceeds. I am sure, for example, that Enrico Fermi, when he discovered the consequences of slow neutron bombardment of atoms -- or Otto Hahn, when he studied the fission of heavy atoms -- did not for a moment think ahead to the Hiroshima bomb, or for that matter, to the difficulties that sooner or later might present themselves in connection with nuclear power. In my view, as long as there are medical advances to be made, and diseases to cure or alleviate, research workers in the biomedical field will continue to explore the promising leads.

Before considering the many beneficial aspects of genetic engineering, I would like to continue just a little longer on the topic of the responsibility of the scientist for his own discoveries. I am sure that any reasonable scientist would fight against the use of his research products for thoughtless or criminal ends. Although no set of rules has yet been devised for the control of experimental genetic manipulation of human beings, I would guess that such a code will eventually be devised, and will, of course, depend on the cooperation of investigators in the field. The unfortunate fact is that the public cannot imagine the rate of progress in a field such as genetic engineering, and it might be quite difficult to devise supervisory rules and regulations that would be sufficiently flexible and au courant to keep up with advances in knowledge and clinical trial. Even with a high level of understanding and cooperation, one can imagine situations in which control would be deliberately sabotaged. Consider, for example, the deranged scenarios that existed in the concentration camps in World War II. If current techniques had been easily available, experimenters involved with captives would almost certainly have tried the modification of human fertilized eggs by exposure to purified genes or to heterogeneous mixtures of DNA fragments. This technique which, at the present time, is somewhat limited by the shortage of normally shed ova, could easily be speeded up by the use of ova obtained from ovaries following surgical procedures. I apologize for such a gory example, but I do feel that rules will have to be promulgated, and some world-wide control system will have to be devised to restrict misuse. At the moment, world peace and the Golden Rule are about all we can suggest. I must add that, even though I feel that regulations must be invented, I do not predict more than mild success. The situation is very much a case of Murphy's Law, which states that if something bad can happen, given enough time, it will.

For a change in pace, let me review some of the good things that have happened as the result of the development of the very sophisticated procedures of gene cloning in bacterial cells. The procedures for the controlled introduction of specific human genes in rapidly growing species such as Eschericia coli, which can subsequently manufacture and secrete the material of interest, are now the basis of a flourishing industry involved in the production of various peptides and proteins that can serve as weapons against human disease with essentially no risk. One very popular item of interest, at present, is the protein known as interferon, which is produced by a number of different types of cells in the human body when these cells have been exposed to viruses. My colleagues and I spent about ten years on the isolation and purification of interferon from human cells in culture, but the introduction of the cloning methods more or less outmoded this more classical approach. When the purified gene for interferon is introduced into the genome of the bacterial cell, along with the proper genetic start signals, the cells secrete fairly large amounts of the substance, and purified interferon can be obtained by relatively simple procedures. Interferon promises to be of use in the control of a number of viral diseases, including hepatitis, conjunctivitis, and possibly some forms of cancer. The availability of interferon also makes possible the large-scale production of antibodies against this substance which can be used to remove interferon from the circulating blood in certain diseases such as lupus and rheumatoid arthritis where the levels are abnormally high, and may be involved, somehow, in the dangerous aspects of these diseases.

Another substance that has been prepared by gene cloning in bacterial cells is insulin. The cloned gene is for human insulin since one of the problems that can arise in diabetes is the dangerous immunological effect of insulin taken from the pancreas glands of other species.

Most of the materials so far produced in bacterial culture have been fairly small proteins or polypeptides. It seems certain that the procedures will be improved to a point where large human proteins can be made in quantity. Many human diseases result from the absence of a particular gene, and therapy for such gene deficiency diseases might well turn out to be the introduction of human proteins made by the cloning method.

In some cases, genetic diseases attributable to the absence of critical genes in the chromosomes of patients involve only one, or a very few tissues. Thus, for example, sickle cell hemoglobin is produced by abnormal cells in the bone marrow, lacking the normal hemoglobin gene. These cells produce a form of hemoglobin that causes severe damage, pain, and frequently, early death because of its propensity for precepitating out of solution within the red cells of the patient at low oxygen pressures. A large number of single gene deficiency diseases are known that result from the inability to produce a specific protein product in the cells of one tissue such as brain or pancreas. In such cases, one would like to try to introduce the correct gene into the cells in question without having this genetic material inserted into other cells of the body that are not associated with this particular gene-protein system. Research is underway on techniques that might permit this targeted sort of gene delivery. The experiments are based on the fact that all cells of the body have, on their surfaces, specific receptor sites which can be recognized in a unique way by the proper molecule. One could, in principle, attach the missing gene to a substance which would recognize the surface of the cell type in question, and thus deliver the gene to its proper location. This type of manipulation carries with it the possibilities of bad results, as well as good. Should such a circulating gene be taken up by tissues other than the one for which the targeted gene was devised, it could create a genetic defect worse than the defect the gene therapy was intended to correct.

Lewis Thomas, in his book, The Medusa and the Snail, has pointed out that current advances in the understanding of biological phenomena make it possible to begin thinking about a human society free of disease. Because of the nature of science and of scientists, research directed at the achievement of such a medically utopian state will undoubtedly continue in an inexorable (and a scientifically fascinating) way, not only through the use of the newer methodologies for manipulating and modulating life, but also through the more classical techniques of synthesis and testing of drugs. However, the concept of a world nearly free of disease, considered in the context of our current sociological inadequacies, is frightening. The uninhibited increase in the population of the world, and the almost inevitable increase in hunger and crowding, are the real problems. It is unfortunate, therefore, that the study of the modulation of human behavior and of the rate of human multiplication are not subjects with the level of popularity enjoyed by biomedical science and the curing of the sick.

The field of biotechnology is most heavily concerned with the bioengineering of bacteria to produce useful items such as interferon. Surprisingly little effort or money are spent on using the new biotechnology in areas of food production and population control. We tend to forget that the number of sick people in the world is really rather small when compared with the number of relatively healthy people who go to bed hungry every night. For this reason, I strongly advocate a greater attention to the application of biotechnology to our food sources. The subject does not have the "crowd appeal" of cancer cures or even "giant mice," but perhaps the manipulation of plant rather than human life might ultimately prove to be the most significant direction for research to take.

Let me return for a moment to my central theme: the misuse -- or overuse -- of scientific discovery. Scientists are motivated, generally, by 1) intellectual interest, 2) the thought of making a living in a pleasant profession, 3) the desire for satisfaction of personal ambitions and the need for accolades, and 4) societal forces most frequently stemming from military and economic pressures. I maintain that we will find it impossible to legislate against scientific research of any particular sort, including genetic engineering, by simply admonishing or lecturing to people who have no real desire to listen. It appears to me that only political, economic, and occasionally, ethnic or religious pressures can force large-scale changes in behavior patterns. It is possible that the physical, mental, and psychological makeup of the human animal is such that there will be no solution to the dilemma of how to preserve the human species in the backwash of his own inventions. One factor that might help is the control of population, and if possible, diminution to a much smaller level than now exists on the surface of the planet. Since it would be preferable to achieve a greatly diminished population by some means other than systematic nuclear bomb-dropping, an international effort to educate the people of the world in the direction of a negative population rate should be a first priority. Parenthetically, there might be considerable resistance to such a move by those whose fortunes depend on an ever greater population of purchasers.

I feel free, in the context of the conference title, to speak of population control because much of the problem might be solved by products of contemporary biomedical research and biotechnology. There is, of course, the eternal problem of people in the impoverished agricultural areas desiring to have large families, particularly strong males with a liking for digging in the fields. We might need entirely new answers to world food production and distribution. In this connection, I am reminded of the conversation I had recently with Professor Dennis Powers, of The Johns Hopkins University, who is intrigued with the use of the growth hormone gene in the production of "giant fish." He points out that numerous countries, including China, Israel, and others raise a great deal of animal protein -- in the form of fish -- in ponds. A beautiful blend of nutritional need and modern bioengineering would be the introduction of the gene for fish growth hormone into the fertilized eggs of the edible species, with the subsequent establishment of a biologically competitive subspecies. In modern biology almost anything goes.

Some months ago, Dr. Esbjornson, our organizer, wrote to each member of the panel, listing some preliminary reflections on the theme of the conference. Many of his reflections took the form of questions which I should like to try to answer along the lines of the remarks I have just made. Dr. Esbjornson asks, "What do we want to know about life processes?" "Everything." He asks, "Are there limits we cannot or should not violate?" I would answer this question "No" in the context of basic research aimed at understanding more about our universe and about the nature of living things. At that time when the <u>application</u> of certain classes of scientific observations is contemplated, careful control by suitable panels of academic, legal and governmental experts should certainly be imposed. "Are we disturbing the universe by our probes?" I would say that we certainly are. Let me once again mention giant mice and nuclear bombs. "Are we capable of carrying the burden of responsibilites for the new knowledge we are gaining?" I would answer, "probably no" to this question. In the short run, and during times when our planet is not being wracked by world wars or devastating epidemics, we seem to be able to manage. I sincerely believe that we can maintain adequate surveillance of the application of bioengineering to human beings so long as the human hunger for power and material gain does not become overwhelming. I think it would be difficult and inadvisable to attempt to control the normal progress of scientific research and application. In my view, the problems that arise because of advances in human knowledge in general, and biotechnology in particular, must be dealt with by those among us who are properly experienced in the moral and legal facets of our society.